PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/50, 9/48

A1

(11) International Publication Number: **WO 99/16443**

(43) International Publication Date: 8 April 1999 (08.04.99)

(21) International Application Number: PCT/FI98/00753

(22) International Filing Date: 24 September 1998 (24.09.98)

(30) Priority Data:
973804 26 September 1997 (26.09.97) FI

(71) Applicant *(for all designated States except US)*: ORION CORPORATION [FI/FI]; Orionintie 1, FIN–02200 Espoo (FI).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HARJULA, Maarit [FI/FI]; Lehtisaarentie 6 B, FIN–00340 Helsinki (FI). LARMA, Ilkka [FI/FI]; Urheilutie 8 D E 18, FIN–02700 Kauniainen (FI). ANTILA, Saila [FI/FI]; Mannerheimintie 146 A 3, FIN–00270 Helsinki (FI). LEHTONEN, Lasse [FI/FI]; Seilimäki 20 H 24, FIN–02180 Espoo (FI).

(74) Agent: ORION CORPORATION; Orion Pharma, Industrial Property Rights, P.O. Box 65, FIN–02101 Espoo (FI).

(81) Designated States: AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ORAL COMPOSITIONS OF LEVOSIMENDAN

(57) Abstract

A composition for oral administration comprising substantially pure crystalline polymorphic form (I) of levosimendan as an active ingredient together with a pharmaceutically acceptable carrier is described. Polymorphic form (I) of levosimendan is rapidly absorbed from the gastrointestinal tract and is useful in the treatment of congestive heart disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

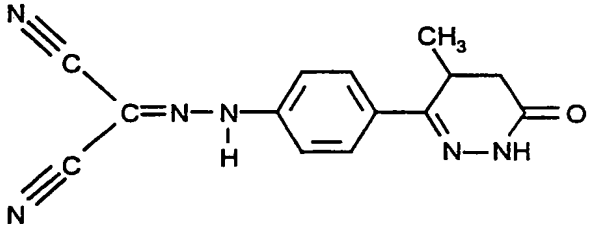
ORAL COMPOSITIONS OF LEVOSIMENDAN

Technical field

The present invention relates to pharmaceutical compositions for oral administration comprising substantially pure polymorphic form I of levosimendan, the (-) enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile, as an active ingredient. Levosimendan is useful in the treatment of congestive heart failure.

Background of the invention

The racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) has been described earlier in the applicant's European Patent No. 383449 B1. It was shown that compound (I) is potent in the treatment of congestive heart failure and has significant calcium dependent binding to troponin.



I

Optically active enantiomers of (I) have been earlier described in the applicant's European Patent No. 565546 B1. It was shown that the cardiotonic potency is predominantly due to the (-) enantiomer of (I), i.e. levosimendan.

Oral administration of levosimendan has proved difficult since levosimendan is susceptible to metabolization in the lower gastrointestinal tract by intestinal bacteria. The metabolites formed in the lower gastrointestinal tract may contribute to the observed side effects of orally administered levosimendan, such as headache and palpitation. Therefore methods and compositions for administering levosimendan orally which would avoid or reduce the accumulation of levosimendan in the lower gastrointestinal tract would be highly desirable.

Summary of the invention

It has now been found that levosimendan is rapidly dissolved and absorbed into plasma from oral compositions which comprise substantially pure crystalline polymorphic form I of levosimendan as the active ingredient. The rapid absorption reduces the accumulation of levosimendan in the lower gastrointestinal tract and thereby reduces gastrointestinal metabolization of levosimendan.

Thus the present invention provides an oral composition comprising a substantially pure crystalline polymorphic form I of levosimendan as the active ingredient together with a pharmaceutically acceptable carrier.

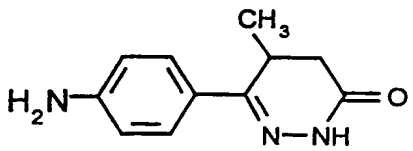
Brief description of the drawings

FIG. 1 is the X-ray powder diffraction pattern in 3 - 33 2θ ° range of the polymorphic form I of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)-phenyl]hydrazono]propanedinitrile

Detailed description

The term "substantially pure crystalline polymorphic form I of levosimendan" means here (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile of which at least about 90 %, preferably at least 95 %, and more preferably at least 99 % per weight is in the form of crystalline polymorph I.

Crystalline polymorphic form I of levosimendan can be prepared from compound (II) by resolution of the racemic material in two different synthesis stages.



II

The racemic compound (II) can be synthesized by methods known in the literature (J. Med. Chem., 17, 273-281 (1974)).

The initial resolution step comprises reacting the racemic mixture of (II) with D- or L-tartaric acid in ethyl acetate solvent. Advantageously the ethyl acetate solvent contain from 0 to about 6 w-%, preferably from 2 to 4 w-%,

more preferably about 3 w-%, of water. It is preferred to use D- or L-tartaric acid and compound (II) in about equimolar amounts. The diastereomeric salts of (-) 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone with D-tartaric acid or corresponding (+) 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone with L-tartaric acid crystallize from ethyl acetate in good yield. The crystalline diastereomeric salt can be filtered and the free base liberated by basifying the salt with e.g. potassium carbonate solution or ammonia. The mother liquid can be recovered after filtering and be further treated in order to recover the enantiomer which was not previously removed by precipitation. The treatment may comprise e.g. cooling the mother liquid and recovering the resulting crystalline diastereomeric salt.

Typically the product obtained by the above described method contains about 90 w-% of the desired enantiomer of (II). The purity of the product can be increased to about 96 w-% by recrystallization. Acetonitrile is the preferred recrystallization solvent. For example, the product which is enriched in (-) enantiomer is recrystallized by adding the product to acetonitrile solvent, refluxing the mixture and filtering precipitate. The filtrate is concentrated, if necessary, and cooled in order to crystallize the (-) enantiomer of (II).

Partial resolution of compound (II) can be obtained using other solvent systems than ethyl acetate. Such solvents include isopropanol, isobutanol, isopropyl acetate, butyl acetate, acetone and acetonitrile. Also the use of other resolving acids than D- or L-tartaric acid can result in partial resolution of compound (II), e.g. benzoic acid or sulphuric acid. However, the method of using D- or L-tartaric acid in ethyl acetate or aqueous ethyl acetate solvent provides the highest optical purities for compound (II).

The (-) enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) is prepared from 6-(4-amino-phenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone (II) which is enriched in (-) enantiomer by allowing (II) to react with sodium nitrite and malononitrile in acidic conditions as described in EP 383449 B1. Compound (I) which is enriched in (-) enantiomer is then recovered.

The minor component in a partly enriched enantiomer mixture of compound (I) can be filtered out from acetone leaving the rest of the major component in solution. This allows recovering the substantially pure (-) enantiomer of (I) from the mother solution by crystallization.

Thus, the previously recovered compound (I) which is enriched in (-) enantiomer is suspended in acetone solvent, which preferably contains up to 2 w-% of water. The mixture is refluxed and the precipitate is filtered. The filtrate is then concentrated, if necessary, and cooled to about 0 - (-5) °C. The precipitated crystalline (-) enantiomer of (I) is recovered. The product contains typically more than 99 w-% of the desired (-) enantiomer of (I).

The crystallographical purity of the above obtained polymorphic form I of compound (I) can be, if desired, improved by heating the obtained (-) enantiomer of (I) at a temperature of at least about 70 °C for a time period necessary for the formation of crystallographically pure polymorphic form I. The suitable temperature is typically within the range of 70 - 160 °C, preferably 80 - 130 °C. The time period is typically within the range of 1 - 48 h, preferably 4 - 24 h. This treatment may be part of the drying process of the product and may be carried out in vacuum.

The polymorphic form I of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile is characterized by the X-ray crystallography. The X-ray powder diffraction pattern of the polymorphic form I in 3 - 33 2θ ° range is in Figure 1 and the crystallographic data in Table 1.

The diffraction pattern was measured by the X-ray powder diffraction (XRPD) equipment, Siemens D 500 (Siemens AG, Karlsruhe, Germany). A copper target X-ray (wavelength 0.1541nm) tube was operated with the pow r of 40kV x 40 mA. For X-ray powder diffraction analysis the samples were mounted by loosely pressing about 500 mg of the powder to the specific cylindrical sample stage which has a diameter of 20 mm and height of approximately 2 mm. Mathematical evaluation of diffraction patterns was performed with aid of Diffrac AT V3.1 software package. Main characteristics of the diffraction patterns as 2θ–values and relative peak intensities were produced as out-put data.

Table 1. X-ray diffraction angles (2θ °) and corresponding relative intensity values (only %-values > 5%) of polymorphic form I.

2θ angle(°)	Relative intensity (%)
8.7	5
9.5	23
12.2	34
15.4	25
15.9	40
17.7	72
18.4	8
19.2	9
20.3	27
21.4	8
21.8	8
23.1	36
24.6	12
25.7	100
27.4	64

The relative intensity values may vary remarkably because of different orientation of crystals. Therefore, the relative intensity values given in Table 1 can be regarded as representative only for, e.g. non-micronized powder.

The present invention provides a composition for oral administration comprising a substantially pure crystalline polymorphic form I of levosimendan as the active ingredient together with a pharmaceutically acceptable carrier. The compositions of the invention include solid compositions in the form of e.g. tablets, dragees, capsules, powders and granules. The contents of the active compound in the composition of the invention is generally from about 0.01 to 100 %, preferably from 0.1 to 20 %, most preferably from 0.5 to 10 % per weight. In general levosimendan is administered orally to man in doses from about 0.1 to 10 mg, preferably from 0.5 to 5 mg once or several times a day depending on the age, body weight and condition of the patient.

The compositions of the invention can be prepared by mixing substantially pure crystalline polymorphic form I of levosimendan together with pharmaceutically acceptable carriers. Pharmaceutically acceptable carriers include those which are used according to standard pharmaceutical practice and which are compatible with the active ingredient. For oral administration in

tablet form, suitable carriers and excipients include lactose, corn starch, magnesium stearate, calcium phosphate and talc. For oral administration in capsule form, useful carriers and excipients include lactose, corn starch, magnesium stearate and talc. Capsules can be prepared by mixing the active ingredient with the carriers and excipients and placing the powdery mixture in capsules, e.g. hard gelatin capsules. Tablets can be prepared by mixing the active ingredient with the carriers and excipients and compressing the powdery mixture into tablets.

The following examples are meant to further illustrate the invention without limitation.

EXAMPLE 1. Pharmaceutical example

Hard gelatin capsule size 3	
Levosimendan (polymorph I)	2.0 mg
Lactose	198 mg

EXAMPLE 2. Pharmacokinetic study

Pharmacokinetic parameters of two different polymorphs, (I) and (II), of levosimendan in healthy volunteers after a single oral dose of 2 mg of levosimendan capsule was studied. The formulations of hard gelatin capsules (size 3) A and B were the following:

Capsule A:	
Levosimendan (polymorph I)	2.0 mg
Lactose	198 mg

Capsule B	
Levosimendan (polymorph II)	2.0 mg
Lactose	198 mg

The results of the pharmakinetic study are presented in Table 2 and 3. The small value of T_{max} indicates rapid absorption of the drug into plasma.

TABLE 1. Pharmacokinetic parameters after a single oral dose of capsule A to healthy subjects 1-9.

Subject	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC (ng h/ml)
1	67.9	0.75	0.82	97
2	-	-	-	-
3	82.0	1.00	0.83	166
4	-	-	-	-
5	112	0.33	0.76	131
6	92.1	0.75	0.86	155
7	79.9	1.25	0.81	185
8	172	0.50	0.81	191
9	125	0.50	0.88	135
Mean	104	0.73	0.82	151
SD	36	0.32	0.04	33
SEM	13	0.12	0.01	12

TABLE 2. Pharmacokinetic parameters after a single oral dose of capsule B to healthy subjects 1-9.

Subject	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC (ng h/ml)
1	91.1	0.50	0.78	109
2	76.0	1.00	0.65	123
3	112	1.00	0.72	151
4	111	0.33	0.84	134
5	88.4	1.50	0.67	174
6	150	0.50	0.77	178
7	-	-	-	-
8	89.7	0.75	0.86	176
9	45.0	2.50	0.76	121
Mean	95	1.01	0.76	146
SD	31	0.71	0.07	28
SEM	11	0.25	0.03	10

EXAMPLE 3. Preparation of (-)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone

100 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone was added to 2997 ml of ethyl acetate, 94.4 ml of water, 77.8 g of D-tartaric acid and 1.0 g of D-tartaric salt of (-)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone under nitrogen. The mixture was stirred in 25 °C for 1.5 h. The mixture was then heated to 65 °C and stirred for 2 h. The precipitate was filtered hot and washed with 561 ml of ethyl acetate. The precipitate was mixed with 400 ml of water and pH of the mixture was adjusted to 9 - 10 with NH_3. The mixture was cooled to 0 °C and stirred for 2 h. The precipitate was filtered, washed three times with 322 ml of cold water and dried in vacuum in 50 °C. Yield was 35 g and the ratio of (- / +) enantiomers 93 / 7 %. The product (35 g) was further added to 777 ml of acetonitrile and 2.0 g of celite under nitrogen. The precipitate was filtered hot and washed with 33 ml of acetonitrile which was added to the filtrate. 253 ml of acetonitrile was distilled from the filtrate and the remaining mixture was cooled to -5 °C. The precipitate was filtered, washed with 76 ml of acetonitrile and dried in vacuum in 50 °C. Yield 24.5 g. Ratio of (- / +) enantiomers 96 / 4 %.

EXAMPLE 4. Preparation of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile

The 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone obtained in previous Example with (- / +) resolution % of 96 / 4 was treated with sodium nitrite and malononitrile as described in the European Patent No. 383449 B1. 10 g of the recovered [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile with (- / +) resolution % of 96 / 4 was added to 150 ml of acetone, 0.9 ml of water, 0.2 g of activated carbon and 0.4 g of Celite. The mixture was refluxed for 1 h and filtered hot. The precipitate was washed with 10 ml of hot acetone which was added the to the filtrate. The filtrate was refluxed for 30 min. 61 ml of acetone was distilled from the filtrate and the remaining mixture was cooled to 0 - (-5) °C. The mixture was filtered and washed with 10 ml of cold acetone. The crystalline product was dried in vacuum in 100 °C for 5 h. The product contained over 99 % of the desired (-) enantiomer and the yield was 6.8 mg. The product was substantially pure crystalline polymorphic form I.

The enantiomeric purities of the products were determined by the high performance liquid chromatography (HPLC). The enantiomers of compound (II)

were separated by using a cellulose-type chiral column (Chiralcel OJ 25 x 0.46 cm). The mobile phase consisted of ethanol. The flow rate was 0.5 ml/min. The enantiomers of compound (I) were separated by using a ß-cyclodextrin column (Cyclobond I Beta, 4.6 x 250 mm). The mobile phase consisted of 36 % methanol in water buffered to pH 6.0 with 1 % triethylammonium acetate. The flow rate was 0.8 ml/min.

CLAIMS

1. A composition for oral administration comprising substantially pure crystalline polymorphic form I of levosimendan as an active ingredient together with a pharmaceutically acceptable carrier wherein the crystalline polymorphic form I of levosimendan is characterized by the X-ray diffraction pattern having the following peak positions:

2θ angle(°)
8.7
9.5
12.2
15.4
15.9
17.7
18.4
19.2
20.3
21.4
21.8
23.1
24.6
25.7
27.4

2. A composition of claim 1 in the form of tablets, dragees, capsules, powders or granules.

3. A composition of claim 1 or 2 wherein the amount of the active ingredient in the composition is from 0.1 to 20 % per weight of the composition.

4. A composition of claim 3 wherein the amount of the active ingredient in the composition is from 0.5 to 10 % per weight of the composition.

5. A composition of any of claims 1-4 wherein the amount of the active incredient is 0.1 to 10 mg.

6. A composition of any of claims 1-5 wherein the pharmaceutically acceptable carrier is lactose.

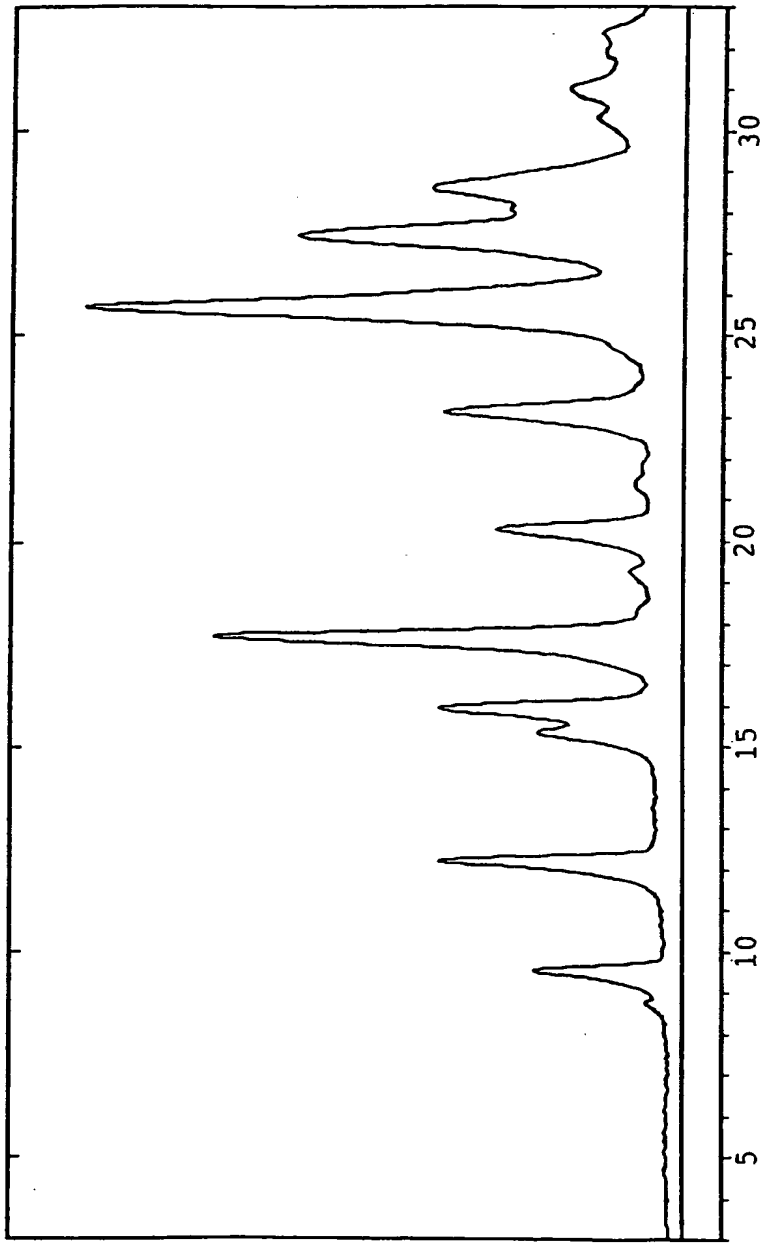


FIG. 1

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/FI 98/00753

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/50 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 12135 A (ORION-YHTYMÄ OY,FI) 23 July 1992 cited in the application see the whole document	1-6
A	EP 0 383 449 A (ORION-YHTYMÄ OY,FI) 22 August 1990 cited in the application see the whole document	1-6
A	WO 93 21921 A (ORION-YHTYMÄ OY,FI) 11 November 1993 see the whole document	1-6
A,P	WO 98 01111 A (ORION-YHTYMÄ OY,FI) 15 January 1998 see the whole document	1-6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 1999	13/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ..tional Application No
PCT/FI 98/00753

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 97 35841 A (ORION-YHTYMÄ OY,FI) 2 October 1997 see the whole document -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/FI 98/00753

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9212135 A	23-07-1992	AT 119525 T	15-03-1995
		AU 645399 B	13-01-1994
		AU 1153592 A	17-08-1992
		BG 97915 A	25-04-1994
		CA 2099262 A	04-07-1992
		CY 1878 A	05-04-1996
		DE 69201640 D	13-04-1995
		DK 565546 T	22-05-1995
		EP 0565546 A	20-10-1993
		ES 2070627 T	01-06-1995
		FI 932618 A	09-06-1993
		FI 972077 A	15-05-1997
		GB 2251615 A,B	15-07-1992
		HK 117395 A	28-07-1995
		HU 64754 A	28-02-1994
		IE 72101 B	12-03-1997
		IL 100553 A	31-12-1995
		IL 114028 A	12-09-1996
		JP 9183767 A	15-07-1997
		JP 2635445 B	30-07-1997
		JP 6504275 T	19-05-1994
		LV 11174 A	20-04-1996
		LV 11174 B	20-12-1996
		NO 300682 B	07-07-1997
		PL 169435 B	31-07-1996
		PL 169415 B	31-07-1996
		US 5424428 A	13-06-1995
		US 5569657 A	29-10-1996
		US 5512571 A	30-04-1996
EP 383449 A	22-08-1990	AT 127456 T	15-09-1995
		AU 619648 B	30-01-1992
		AU 4929690 A	16-08-1990
		CA 2009678 A,C	11-08-1990
		CN 1044811 A,B	22-08-1990
		DD 293112 A	22-08-1991
		DE 69022078 D	12-10-1995
		DE 69022078 T	22-02-1996
		DK 383449 T	02-01-1996
		ES 2078939 T	01-01-1996
		FI 96511 B	29-03-1996
		GB 2228004 A,B	15-08-1990
		GR 3017510 T	31-12-1995
		JP 2288868 A	28-11-1990
		LT 1233 A,B	25-04-1995
		NO 178067 B	09-10-1995
		PT 93111 A,B	31-08-1990
		RU 2048467 C	20-11-1995
		SU 1836362 A	23-08-1993
		RU 2068844 C	10-11-1996
		US 5019575 A	28-05-1991
		US 5185332 A	09-02-1993
		US 5122524 A	16-06-1992
WO 9321921 A	11-11-1993	GB 2266841 A	17-11-1993
		AU 4262793 A	29-11-1993
		BG 61678 B	31-03-1998
		BG 99164 A	28-08-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ..onal Application No
PCT/FI 98/00753

Patent document cited in s arch report	Publication date	Patent family member(s)	Publication date
WO 9321921 A		BR 9306314 A	30-06-1998
		CA 2134972 A	11-11-1993
		CZ 9402720 A	15-02-1995
		EP 0639074 A	22-02-1995
		FI 945052 A	27-10-1994
		HU 68956 A	28-08-1995
		JP 7506354 T	13-07-1995
		NO 944145 A	31-10-1994
		NZ 252693 A	27-07-1997
		SK 132494 A	08-11-1995
		US 5512572 A	30-04-1996
WO 9801111 A	15-01-1998	AU 3345997 A	02-02-1998
WO 9735841 A	02-10-1997	AU 2162697 A	17-10-1997